EXHIBIT 20

Dementia, stroke, and vascular risk factors; a review

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Interest in dementia has increased over the past few decades. Stroke is an important cause of cognitive problems. The term vascular cognitive impairment is now used to describe dementia attributed to stroke or deep white matter lesions detected on imaging. Although vascular cognitive impairment is increasingly diagnosed, Alzheimer's disease remains the most common dementia worldwide. The relationship between Alzheimer's disease and vascular cognitive impairment is unclear, although there exists significant overlap, which prompts physicians to consider them opposite ends of a disease spectrum, rather than separate entities. There is also substantial evidence that stroke risk factors such as hypertension, diabetes; lipid disorders, etc. are independently associated with an increased risk of Alzheimer's disease and vascular cognitive impairment. Evidence suggests that these risk factors have a cumulative effect on Alzheimer's disease development but not on vascular cognitive impairment. This is more marked in Alzheimer's disease patients in the presence of the ε4 allelic variant of apolipoprotein E. How these risk factors increase the risk of dementia is largely unknown. Physicians must be aware that stroke causes dementia; that vascular risk factors appear to be independent risk factors in developing dementia, and that post-stroke care must include cognitive assessment.

Key words: AD, dementia, stroke, vascular risk factors, VCI

Introduction

In 2005, global stroke incidence was estimated at 16 million cases and projected at 23 million by 2030 (1). Stroke incidence and mortality decline in high-income countries but increase in middle- and low-income countries of the world (2,3); the decrease in high-income countries is a reflection of better healthcare standards and intervention strategies. However, at least one study demonstrates that these survival rates translate to an increased number of cognitively impaired stroke survivors (4).

Dementia affects approximately 5% of the population under the age of 65 years. By the age of 85, incidence increases to effect 25% of the population. These data are drawn from population studies in Europe (5). It is difficult to makes similar estimates for middle- and low-income regions of the world as there are little data. Subsequently, it has been conjectured that the number of demented patients worldwide will quadruple over the next three decades to reach approximately 81 million by 2040, with two-thirds in the developing world (6).

Research linking stroke and dementia has focused on shared vascular risk factors, ameliorated by lifestyle modification or medication. The most important risk factor, aging, is beyond any such measures at present. The number of elderly is expected to increase exponentially in the next few decades; the largest increase will again be seen in the developing world (7). We face an unholy trinity of aging, stroke, and dementia.

Stroke has long been associated with dementia (8), but the relationship remains contentious and unproven.

Many questions raised in research are largely unanswered: Is dementia following stroke solely explained by the area or size of the infarct?
Does an infarct trigger specific neuropathological changes, or does the presence of stroke hasten latent neurodegeneration?
Are vascular risk factors implicated in dementia merely because they increase the risk of stroke, or are there other means by which they act?

In this review, we attempt to clarify the current understanding of the association between stroke and dementia starting with current nomenclature, a brief look at the histopathological and genetic aspects, established incidence and prevalence studies linking stroke and dementia, epidemiological links between vascular risk factors and the risk of dementia, and effect of treatment of vascular risk factors on dementia. In recent years, the amount of research conducted to address these issues has been substantial.

Search strategies

We searched for articles in PubMed using the following search terms: stroke, dementia, Alzheimer's disease (AD), vascular

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Systematic Review

R. Sahathevan *et al*.

dementia (VaD), poststroke dementia (PSD), multi-infarct dementia, vascular cognitive impairment (VCI), amyloid, vascular risk factors, hypertension, diabetes mellitus (DM), hypercholesterolaemia, atrial fibrillation (AF), smoking, homocysteine, and apolipoprotein E (ApoE). Articles were limited to reviews and mini-reviews published in English. Selected searches were carried out by hand on the references of major reviews published after 2000.

Nomenclature

The varying terms used to describe cognitive impairment is confusing, particularly for cognitive impairment following stroke. Cases of dementia are labelled as either AD or VCI. Less common forms of dementia include frontotemporal dementias (FTD), dementia with Lewy body disease, Parkinson's related dementia, etc. These conditions are defined using unique clinical features, and are diagnosed based on specific diagnostic criteria, neuroimaging, and neuropathological features.

Based on Diagnostic and Statistical Manual (DSM-IV) criteria (9), a diagnosis of dementia must fulfil the following criteria:

• Cardinal symptom of memory impairment with involvement of one additional cognitive domain (language, motor activity, recognition, or executive function)
• Impairment that is severe enough to impact on daily social or occupational function, and
• Deterioration from a previously higher level of function.

The most common form of dementia is thought to be AD which constitutes approximately 50–70% of all dementias (6). The next most common dementia is VCI which makes up 15–25% of some pathological series (10). There is increasing evidence of a significant overlap between AD and VCI. This condition is referred to as mixed dementia (MD). One pathological case series has shown that MD was responsible for approximately 50% of dementias diagnosed in life (11). If these figures were a true indication of dementia numbers, it would cause a paradigm shift in the diagnostic and clinical approach to dementia. The existence of MD is partly responsible for increased research into the impact of vascular risk factors in dementia.

AD diagnosis is outlined in the National Institute of Neurological Disorders and Stroke-Alzheimer's Disease and Related Disorders (NINCDS-ADRDA) working group (12) (Table 1); it is used in conjunction with the DSM-IV (13). Diagnosis of VCI is yet to be defined by consensus criteria. Best approximation for the diagnosis of cognitive impairment following a stroke is based on criteria outlined by the National Institute of Neurological Disorders and Stroke, and Association Internationale Pour La Recherché et l'Enseignement en Neurosciences working group (14) (Table 2), also used in conjunction with the DSM-IV. The NINCDS-ADRDA diagnostic criteria for AD were recently reviewed to include a clear definition of mild cognitive impairment (MCI) and support the

role of ancillary imaging such as positron emission tomography (PET) (15). AD and VCI are simply distinguished based on memory impairment. Clinically, AD is characterized by deficits of memory involving recall of events or people (episodic memory) or factual knowledge (semantic memory) (16). VCI is usually associated with deficits of executive function, which might be demonstrated by planning an activity or ordering food from a menu (17). The definitive diagnosis of either AD or VCI remains the histopathological examination.

One of the first terms used to describe dementia was multi-infarct dementia (18), which was then supplanted by VaD (19). The term currently favoured in the literature is VCI. VCI is a general term encompassing any form of cognitive deficit following and attributable to stroke. The term was coined by Bowler and Hachinksi (20) but best defined by O'Brien *et al.* (17) to encompass PSD, VaD, MD as defined previously, and vascular MCI (Table 3). Hachinski *et al.* used the term VCI exclusively in documenting the proceedings of the workshop convened to discuss harmonization of standards in research into cognitive decline and stroke (21). More recently, the American Heart Association and the American Stroke Association jointly issued a scientific statement on vascular disease and cognitive dysfunction that also endorsed use of the term VCI (22).

Pathological changes of AD, VCI, and genetic factors

There are many theories regarding the cause of AD. Proponents of the amyloid cascade hypothesis argue that amyloid deposition is the initial insult that ultimately leads to neuronal damage, cognitive impairment, and, ultimately, AD (23–26). Those who favour the vascular hypothesis suggest that a combination of cerebral hypoperfusion, the culmination of vascular pathology, and senescence leads to neuroglial energy crisis, neuronal damage, cognitive damage, and, ultimately, AD (27–29).

AD and VCI are associated with specific pathological changes. Hallmarks of AD are the deposition of extracellular neuritic plaque (NP) and intracellular neurofibrillary tangles (NFT). NP are made up of aggregated amyloid-beta (Aβ) fibrils. These fibrils are the product of sequential cleavage of amyloid precursor protein (APP) by beta and gamma secretase. The proteolytic action of beta and gamma secretase preferentially generates Aβ_{1-42} fibrils that are more hydrophobic and prone to aggregation. Autosomal dominant mutations of the APP gene on chromosome 21, the presenilin-1 gene on chromosome 14, and presenilin-2 gene on chromosome 1 are the main genetic abnormalities associated with familial AD (30). These conditions are rare and constitute less than 5% of all AD cases (31).The presenilins form a part of the gamma secretase complex, but the full extent of presenilin influence on secretase function is not known (32), and genetic abnormalities associated with beta secretase function are yet to be identified.

Systematic Review

Table 1 NINCDS-ADRDA criteria for the diagnosis of Alzheimer's disease (adapted from Dubois (13))
Probable AD: A plus one or more supportive features B,C, D, or E
Core diagnostic criteria Presence of early and significant episodic memory that includes the following: - Gradual and progressive change in memory function over more than six-months   - Objective evidence of impaired episodic memory: recall deficit that does not improve significantly or does not normalize with cueing or recognition testing and after effective encoding of information has been previously controlled, and   - The episodic memory impairment can be isolated or associated with other cognitive changes at the onset of AD or as AD advances.   Supportive features   - Presence of medial temporal lobe atrophy   - Abnormal cerebrospinal fluid biomarker   - Specific pattern on functional neuroimaging with PET   - Proven AD autosomal dominant mutation within the immediate family   Exclusion criteria History   - Sudden onset, and   - Early occurrence of gait disturbance, seizures, or behavioural changes   Clinical features   - Focal neurological features including hemiparesis, sensory loss, visual field deficits, and   - Early extrapyramidal signs   Other medical disorders severe enough to account for memory and related symptoms   - Non-AD dementia   - Major depression   - Cerebrovascular disease   - Toxic and metabolic abnormalities, and   - MRI changes in the medial temporal lobes that are consistent with infectious or vascular insults
Definite AD
Clinical and histopathological (brain biopsy or autopsy) evidence of disease as required by the NIA-Reagan criteria for the post-mortem diagnosis of AD; both must be present Clinical and genetic evidence (mutation on chromosome 1, 14, or 21); both must be present
AD, Alzheimer's disease; MRI, magnetic resonance imaging; NINCDS-ADRDA, National Institute of Neurological Disorders and Stroke-Alzheimer's Disease and Related Disorders.

NFT are intraneuronal protein aggregates of hyperphosphorylated tau proteins (33). While there are known mutations of tau protein, none are known to be associated with AD (34,35). Some researchers suggest that tau hyperphosphorylation is the initiator of AD pathology rather than amyloid deposition. We now know that NFT formation occurs later in the course of the disease and does not precede $A\beta$ deposition (36). Mutation of the tau protein is mapped to chromosome 17 (37) and associated with a group of dementia disorders that have distinct clinical, neuroimaging, and pathological features. The dementias are sometimes collectively termed tauopathies and include FTD, corticobasal degeneration, and progressive supranuclear palsy (38).

Apolipoprotein E (ApoE) allelic variants are associated with increased risk of sporadic AD, which is commonly seen after 65 years of age.

Categorization of VCI by pathological change is more difficult, reflecting the heterogeneity of the condition itself. The effects of vascular pathology on clinically apparent cognitive impairment are dependent upon morphology (focal or multifocal; large or small vessel), volume of brain destruction, location and number of lesions (39). Histopathology studies also provide crucial information regarding the overlap between AD and vascular lesions. The proportion of patients with both pathologies ranges from approximately 25% (11) to 56% (40) depending on the review. The importance of the overlap of these pathologies is provided by the results of the Nun Study. Snowdon and colleagues demonstrated that if vascular lesions were present in the thalamus, basal ganglia, or deep white matter, the amount of NP required to cause cognitive impairment was reduced (41).

Epidemiological evidence: dementia following stroke

Evidence of dementia following stroke is provided by hospital- and community-based studies. The best evidence of a link is provided by longitudinal case-control or cohort studies in cognitively normal individuals who suffered a first-ever stroke and then developed dementia.

One of the first studies to assess the effect of stroke on dementia was a hospital-based assessment of previously

Systematic Review

Table 2 NINDS-AIREN criteria for the diagnosis of vascular dementia (adapted from Roman *et al.* (14))

Probable vascular dementia: all of the following

- Dementia as defined in the DSM-IV
- Cerebrovascular disease defined by the presence of focal signs on neurological examination (hemiparesis, lower facial weakness, Babinski sign, sensory deficit, hemianopia, and dysarthria consistent with stroke) and evidence of relevant changes on brain imaging either on CT or MRI (multiple large vessel infarct, single strategic infarct, lacunar infarcts or extensive white matter lesions either singly or in combination), and
- A relationship between the two disorders above manifested or inferred by the presence of one or more of the following:
  - Onset of dementia within three-months following a recognized stroke, and
  - Abrupt deterioration of cognitive functions or fluctuating, stepwise progression of cognitive deficits.

Clinical features consistent with the diagnosis of probable vascular dementia include the following:
- Early presence of gait disturbance
- Unsteadiness and frequent unprovoked falls
- Urinary symptoms not explained by urologic disease
- Pseudobulbar palsy, and
- Personality and mood changes including abnormal executive function.

Features that make the diagnosis of vascular dementia uncertain or unlikely:
- Early onset of memory deficit and progressive worsening of memory deficit and progressive worsening of memory and other cognitive functions such as language, motor skills, and perception in the absence of corresponding focal lesions on brain imaging
- Absence of focal neurological signs other than cognitive disturbance, and
- Absence of cerebrovascular lesions on brain imaging.

Possible vascular dementia

Presence of dementia (DSM-IV) with focal neurological signs in patients in whom:
- Brain imaging studies to confirm definite cerebrovascular disease are missing
- There is absence of a clear temporal relationship between dementia and stroke, and
- There is subtle onset and variable course of cognitive deficits and evidence of relevant cerebrovascular disease.

Definite vascular dementia

Clinical criteria for probable vascular dementia with:
- Histopathological evidence of cerebrovascular disease obtained on biopsy or autopsy
- Absence of neurofibrillary tangles and neuritic plaque exceeding those expected for age, and
- Absence of other clinical or pathological disorder capable of producing dementia.

NINDS-AIREN, National Institute of Neurological Disorders and Stroke, and Association Internationale Pour La Recherché et l'Enseignement en Neurosciences.

Table 3 Classification of vascular cognitive impairment as defined by O'Brien *et al.* (17)

Classification and causes of sporadic vascular cognitive impairment

- Poststroke dementia
- Vascular dementia
- Multi-infarct dementia (cortical vascular dementia)
- Sub-cortical ischaemic vascular dementia
- Strategic-infarct dementia
- Hypoperfusion dementia
- Haemorrhagic dementia
- Dementia caused by specific arteriopathies
- Mixed AD and vascular dementia
- Vascular mild cognitive impairment

AD, Alzheimer's disease.

normal patients who suffered a stroke compared to age-matched, stroke-free controls (42). The stroke patients were nine times more likely to have dementia compared to controls at three-months, but they only approximately five times as likely to exhibit dementia when assessed at 4·5 years (42,43).

One of the first population-based studies to assess the relationship between stroke and dementia was conducted in Rochester, Minnesota (44). Nine hundred seventy-one cognitively normal patients with first-ever ischaemic stroke were enrolled after medical record review. Assessment three-months poststroke indicated that stroke survivors had a nine-fold increase in dementia compared to the general population, although this increase was not sustained over time. Sustained risk of dementia following stroke was twice that of the general population over a five-year period. There was higher risk of dementia in recurrent strokes.

The Rotterdam study is a large population-based cohort study of age-related disorders in over 10 000 older individuals who were stroke free and cognitively normal at baseline (45,46). The findings of the study suggests that stroke doubles the risk of dementia, but that prestroke cognitive decline did not have bearing on the development of cognitive deficit (47).

Determining prevalence and incidence of dementia based on individual hospital- or community-based studies is unlikely to give an accurate estimate of the condition given patient heterogeneity and poor generalization of derived data. Pooled analysis will provide more accurate estimates.

Pendlebury and Rothwell (48) showed that differences in cognitive outcomes were primarily due to heterogeneity of study design. There were higher rates of dementia in hospital-based studies possibly due to the inclusion of patients with prior stroke or cognitive impairment. They found that one in 10 patients suffer dementia after a first-ever stroke. The authors also surmise that the primary cause of dementia is stroke itself. While vascular risk factors were predictive of the risk of dementia, they conferred little in terms of absolute risk of dementia. Rather they contributed to the risk of stroke and its recurrence. Recurrent stroke was found to confer substantial risk to developing dementia. Based on pooled analysis of

the various epidemiological studies reviewed, the authors state that one in three patients who suffer a recurrent stroke will suffer dementia.

Savva and Stephan (49) made two age-specific conclusions in their meta-analysis. First, stroke doubled the risk of dementia in those above age 65. Second, stroke survivors who do not develop dementia by the age of 85 have no added risk of developing dementia compared to stroke-free individuals of the same age. They found that prestroke cognitive function was determined to be a risk factor in developing dementia.

The authors of both reviews concurred on the importance of the actual stroke in the development of PSD. They also agreed that cognitive impairment was more likely to occur in the period soon after the incident stroke. The apparent lack of effect caused by vascular risk factors in these two reviews is perhaps due to the design of the individual studies, which were primarily aimed at determining the effect of stroke on dementia. To determine the effect of vascular risk factors, we turn to studies that were designed to primarily assess the effect of these risk factors on the development of AD or VCI.

Vascular risk factors and dementia

Vascular risk factors increase the formation of atheromatous plaque within the intimal layer of arteries. This may lead to chronic or acute end-organ ischaemia. The exception is AF, which causes acute ischaemia through cardiac emboli. Vascular risk factors may be categorized as nonmodifiable or modifiable. Nonmodifiable risk factors for vascular disease include age, sex, and ethnicity, while the modifiable risk factors include hypertension (50,51), DM (52,53), AF (54,55), cigarette smoking (56), and disorders of lipid metabolism (57). In a recent, multicentre, international case-control study, current smoking, an increased hip–waist ratio, and poor diet were also identified as additional significant risk factors in both ischaemic and haemorrhagic stroke (58). The authors of this study suggest that together, these modifiable risk factors may account for approximately 90% of stroke risk. Other risk factors, such as homocysteine and ApoE, have also piqued the interest of various research groups (59). Any of these conditions could be responsible for cerebral damage. However, do these risk factors lead to cognitive deficit by a secondary mechanism independent of stroke pathology?

The hypothesis that vascular risk factors have a causal effect on dementia is difficult to prove in both AD and VCI. Such research would entail long-term prospective assessment of plausible risk factors in a given cohort population in order to prove a link. Epidemiological evidence that a risk factor for a given condition might play a causal role requires the demonstration that intervention in the form of risk factor modification results in a fall in related incidence rates. The methodology of such a placebo-controlled approach would not withstand current ethical scrutiny as we are now aware of the potentially life-threatening conditions associated with untreated vascular risk factors. The integrity of the conclusion reached in many such studies is also hampered by the variability of assessment of incident dementia and the lack of a neuropathological correlate. Those studies in which authors have applied these criteria are few, and are limited to specific study populations which may raise concerns regarding generalizability of the results (41,60).

Researchers have raised the issue of timing for risk factor assessment and onset of dementia as these risk factors likely exert their effects over a protracted period of time, possibly years before the condition becomes clinically evident. Interestingly, studies designed as long–term, case-controlled, longitudinal assessments with periodic and multiple reviews of subjects are those showing significant relation between risk factors and the development of dementia.

Hypertension

Hypertension is the most common modifiable risk factor for stroke worldwide (61). It is increasingly recognized as a risk factor for the development of dementia. Hypertension exposes cerebral microvasculature to pulsatile pressure and flow that cause tearing of the vascular endothelium and smooth muscle cells leading to lipohyalinosis and fibrinoid necrosis (62). The resultant disruption of perfusion can be acute leading to a lacunar infarct or it may cause chronic ischaemia leading to leukoariosis (otherwise referred to as white matter lesion or WML) which is associated with the development of dementia (63,64).

There are many excellent cross-sectional and longitudinal studies that have explored the relationship of dementia, AD, and VCI to hypertension (65–67). The Honolulu-Asia Aging Study (HAAS) and, its predecessor, the Honolulu Heart Program followed a cohort of Japanese-American males born between 1909 and 1919. Participants had six periodic follow-ups beginning in 1965 with the last documented follow-up in 1999 involving 1890 participants. Systolic and diastolic blood pressure (SBP and DBP) measurements were acquired at all visits with cognitive assessment included during the last three. The results show that untreated midlife hypertension is associated with dementia in later life with a stronger association shown for VCI than AD (60,68). Temporal trajectories for blood pressure from the study show that individuals who developed dementia had generally higher SBP in midlife. The effect was ameliorated by antihypertensive therapy. Raised DBP appeared to be relevant only in the development of VCI and was unaffected by antihypertensive treatment (69).

In the Rotterdam study, participants who had a history of antihypertensive use were less likely to develop dementia when compared to those who had never used an antihypertensive agent but had elevated blood pressure. This translated into an 8% risk reduction per year in people aged more than 75 years of age, while in those less than 75, the reduction was 4%. Similar findings were reported in the development of AD, but the superiority of any single antihypertensive agent was not demonstrated due to the small numbers (70).

In the Gothenburg study, patients with raised SBP and DBP on baseline assessment at age 70 were more likely to develop dementia 10–15 years later (71). The combined Rotterdam-Gothenburg study showed similar findings except in the oldest old (those above 85) who demonstrated an inverse relationship between blood pressure and the incidence of dementia (72).

These studies have been designed to assess the effect of blood pressure on clinically diagnosed dementia. What about utilizing imaging or histopathological examination to elucidate the relationship? Volumetric analysis of WMLs on magnetic resonance imaging (MRI) has been shown to correlate positively with poorer performance in specific cognitive domains in the Framingham study (63). The results of HAAS provide evidence that hippocampal atrophy on brain imaging is associated with untreated hypertension in midlife even after correction for the presence of WML and lacunar infarcts (73). There is further evidence from HAAS of a positive correlation among SBP, DBP, and burden of AD pathology in the brain (74).

These findings suggest that a causative link does exist between hypertension and dementia. In summary, raised SBP and DBP in midlife increases the risk of dementia in later life. Treating hypertension in midlife has a protective effect, but whether this effect is due to blood pressure lowering or use of a specific antihypertensive agent is undetermined. The effect of raised blood pressure on cognitive deficit appears to be less marked in older patients and, in fact, lower blood pressure appears to be associated with dementia. Whether hypotension causes cerebral dysfunction due to hypoperfusion, or whether hypotension is itself an effect of dementia, or senile degeneration, and loss of vascular tone is yet to be determined. There is also strong evidence linking hypertension to imaging abnormalities and histopathological changes associated with dementia.

The argument that treating hypertension might reduce the incidence of dementia is supported by the results of certain randomized control trials. The Perindopril Protection Against Recurrent Stroke (PROGRESS) (75) study was a placebo-controlled trial to assess antihypertensive use (perindopril $\pm$ indapamide) on cognitive decline in patients who had had a stroke or transient ischemic attack (TIA). Combination therapy reduced the risk of developing VCI (relative risk reduction (RRR) = 23% (95% confidence interval (CI) 0–41%)), but treatment with perindopril alone showed no benefit. The Heart Outcomes Prevention Evaluation (HOPE) trial (76) assessed ramipril vs. placebo in patients with vascular disease or vascular equivalent (DM), and showed a significant relative risk reduction in cognitive decline assessed as a secondary outcome (RRR = 0·59 (95% CI 0·37–0·94)) The Systolic Hypertension in Europe (Syst-Eur) trial (77) was a placebo-controlled trial in hypertensive patients above the age of 70 who were treated primarily with nitrendipine with possible addition of enalapril or hydrochlorothiazide. The authors reported that compared with controls, long-term antihypertensive therapy reduced the risk of dementia by 55% from 7·4 to 3·3 cases per 1000 patient-years. There have been similar trials assessing the use of antihypertensive agents either singularly or in combination. These trials have been mostly negative (78–82). A recent meta-analysis of blood pressure lowering in stroke-free individuals showed no benefit on decreasing the incidence of dementia (83).

DM

DM is the most common metabolic disorder in the world. The risk of developing DM is linked to genetic predisposition, obesity, and environmental factors. Similar to the risk for stroke and dementia, the risk of developing DM increases with age. Does DM increase the risk of dementia?

Diabetes may influence cognitive function independent of its role as a vascular risk factor. The metabolic stress caused by hyperglycaemic or hypoglycaemic states and the affect of hyperinsulinaemia have all been suggested as potential causes.

Hypoglycaemia in patients suffering from type 1 and type 2 diabetes is almost always iatrogenic. Significant cognitive impairment is a likely outcome of a severe acute hypoglycaemic episode or repeated sub-acute chronic hypoglycaemia (84). In severe hypoglycaemic attacks, blood glucose levels need to fall below 1·5 mmol/L before neuronal necrosis and electroencephalographic (EEG) silence occur (85). This results in permanent brain damage or death occurring as a result of brain death or cardiac arrhythmias (86). These patients therefore do not fit the diagnostic criteria for AD or VCI mentioned earlier. The role of recurrent hypoglycaemic episodes is controversial as studies have shown positive, negative, and equivocal affects of hypoglycaemia on cognitive outcome (87,88). Interestingly, animal studies have shown improved cognitive function in euglycaemia following repeated induced hypoglycaemia in diabetic rats The authors suggest that this may be a result of improved glucose transport and utilization following repeated hypoglycaemia (89).

Hyperglycaemia is also associated with reduced cognitive ability (90). It is hypothesized that hyperglycaemia may act through advanced glycation end-products (AGE). AGE have been found in both NPs and NFT even in the early stages of AD (91). It is suggested that Aβ activates overexpressed AGE receptors seen in AD brains, thus causing increased oxidative stress and cellular damage (92). Hyperglycaemia in the preclinical stage of type 2 DM may cause hyperinsulinaemia by as much as 10 years (93). It is thought that the increased levels of insulin may inhibit the action of insulin-degrading enzyme (IDE) which is a major protease involved in the clearance of Aβ (94). It has been shown *in vivo* that IDE regulates levels of insulin and Aβ.

There is histopathological evidence of a link between DM and dementia. Results of autopsy and imaging studies from the HAAS have shown that diabetic patients had more evident cerebral amyloid angiopathy, NP, and NFT compared to nondiabetics; they also had greater hippocampal atrophy (95,96).

Systematic Review

Data from the Rotterdam study suggest that DM doubles the risk of AD (relative risk (RR) 1·9 (95%CI 1·2–3·1)) and VCI (RR 2·0 (95% CI 0·7–5·6)) (97). There was a threefold increase in the relative risk in patients who had both clinical AD and cerebrovascular disease. Results from the HAAS show that diabetes increased the risk of VCI (RR 2·3 (95% CI 1·1–5·0)) and AD (RR1·8 (95% CI 1·1–2·9)) based on midlife assessment of diabetic status (95). The researchers also found an increased risk of AD (RR5·5 (95%CI 2·2–13·7)) in patients who were suffering from diabetes and were ApoE ϵ4 positive. In a long-term follow-up study, midlife diagnosis of DM was shown to increase the risk of dementia evaluated 30 years later (RR 2·83 (95% CI 1·40–5·71)) (98). There are also studies that have shown no relationship between AD and DM (99) or have selectively found that DM increases the risk of AD in individuals who are ApoE ϵ4 positive (100).

There is lack of evidence of reduced dementia risk associated with treatment of DM. A Cochrane review by Grimley and Areosa found no link between any particular treatment forms of diabetes or glycaemic control targets in reducing the risk of dementia (101). The peroxisome proliferator-activated receptor agonist rosiglitazone was suggested as a possible treatment for dementia. Efficacy of rosiglitazone was being assessed in the Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) trial (102). However, recent concerns regarding the increased cardiovascular mortality attributed to rosiglitazone and intensive blood sugar control make it less likely that the association will be explored further at this juncture (103).

It appears that DM confers an increased risk for developing dementia of AD-type, VCI, or mixed forms. There is more evidence that AD is affected by DM especially in carriers of the ApoE ϵ4 genotype. The exact mechanism remains unknown. Hyperinsulinaemia is a likely candidate due to its association with insulin resistance and increased adiposity in the early stages of disease. There is no evidence that glycaemic control to specific targets or treatment with any specific antidiabetic agent has a role in preventing dementia.

Lipids

Disorders of lipid metabolism are diverse and are categorized according to clinical phenotype, type of elevated lipid or lipoprotein and heritability patterns. The role of lipids in increasing the risk of dementia is controversial, and the mechanism by which raised cholesterol might lead to dementia is unclear. Raised cholesterol is a known risk factor for the formation of atherosclerotic plaque. Recent evidence indicates that high cholesterol levels may also directly impact upon APP metabolism. Reduction of cholesterol levels have been shown to inhibit beta-secretase activity (104) but increase the activity of alpha-secretase (105), the main proteolytic enzymes involved in APP metabolism. Depletion of intraneuronal cholesterol has also been shown to inhibit Aβ production *in vitro* and *in vivo* (106).

Evidence from long-term longitudinal studies suggests that raised serum cholesterol in midlife increases the risk of AD and VCI in late life. Researchers from the Cardiovascular Risk Factors, Ageing, and Incidence of Dementia (CAIDE) study have shown that midlife cholesterol levels in excess of 6·5 mmol/L are significantly associated with the risk of AD in later life (odds ratio (OR) 2·6 [95% CI 1·2–6·0]) (107). They also showed that hypercholesterolemia and ApoE ϵ4 conferred an additive risk for developing AD. Similar long-term studies in a comparable population yielded an OR of 3·1 (95% CI 1·2–8·5) for the same level of cholesterol measured in midlife (108). In the Kaiser Permanante cohort of patients (109), the effect of increased cholesterol at midlife was evaluated on the development of dementia 30 years later. The patient cohort was more varied with regard to ethnicity. The result suggested a more modest increase (hazzard ratio (HR) 1·66 (95% CI 1·31–2·09)) in the risk of AD in patients who had cholesterol levels in excess of 6·2 mmol/L measured in midlife. There was a similar increase in diagnosis of VCI (HR 1·34 (95% CI 0·87–2·07)).There have also been studies that have shown no association between raised cholesterol and risk of developing AD (110).

The trajectory of serum cholesterol levels appears to be important. The CAIDE (111) and HAAS (112) studies have provided data that serum cholesterol levels progressively decrease from midlife in patients with dementia. The decrease begins many years before clinically evident disease. While a similar decrease in cholesterol levels were noted in the control group, it was not as marked. Histopathological brain changes diagnostic of AD are seen in patients with lipid disorders. Brain examination of patients enrolled in the HAAS study show that raised levels of HDL cholesterol in late life are associated with increased NP and NFT in the hippocampus and neocortex (113). The relationship appeared to be dose dependent.

Treatment of hypercholesterolaemia with Hydroxymethylglutaryl-coenzyme A (HMGCoA) reductase inhibitors (statins) appears to have an effect on reducing the incidence of dementia. Evidence from the Rotterdam study suggests that the use of statins, but not other lipid-lowering agents, reduces the risk of dementia (114). The authors suggest that the anti-inflammatory property of statins might be responsible for the effect seen. However, a meta-analysis by McGuiness showed no evidence that treatment with statins or other lipid-lowering agents had an effect on the development of dementia (115).

Increased levels of cholesterol in midlife appear to increase the risk of developing both AD and VCI in later life. Similar to the observation in DM patients, the presence of the ApoE ϵ4 genotype increases the risk of developing AD. The decrease of cholesterol levels seen in patients with AD is of interest. However, does this decrease indicate a part of the disease process or reflect poorer nutritional status of dementing and elderly patients? This warrants further research. The use of statins was shown to have a positive effect on decreasing the

risk of dementia in the Rotterdam study. Whether this is due to actual lowering of cholesterol levels or the anti-inflammatory properties of statins as suggested by the authors is unclear.

AF

AF is a common arrhythmia associated with ischaemic or senile degeneration of cardiac conduction and hypertension. The risk of developing AF increases with age and is more common in males (116,117). Chronic AF is known to be associated with an increased incidence of stroke, heart failure, and increased mortality and morbidity independent of these conditions (118,119).

AF impacts the development of cognitive impairment. In the Rotterdam study, not only was AF more common among subjects with cognitive impairment (OR 2·3; 95% CI 1·4–3·7), it was shown to be an independent risk factor for the development of AD and VCI. Increased risk was not explained by the risk of stroke associated with AF (120,121). A more recent prospective study of 37 000 older patients (mean age 60 ± 17·9) has shown a higher incidence of cognitive impairment in subjects who developed AF over a five-year follow-up period (122). However, a similar study in patients aged 75 and above did not show an association between AF and either VCI or AD (123). There is further evidence of hippocampal atrophy associated with memory function impairment in patients who had chronic AF but were clinically and radiologically stroke free (124).

The mechanism by which AF increases the risk of cognitive impairment independent of stroke is unclear. Proposed mechanisms include cerebral hypoperfusion associated with low cardiac output in patients with rapid ventricular response, strokes that are clinically silent, or strokes due to microemboli. There is at present no evidence that treatment of AF by either rate or rhythm control or prevention of emboli via anticoagulation reduces the risk of cognitive impairment.

The impact of AF on the development of dementia is potentially very interesting. There are few long-term studies that have assessed cognitive outcome in patients with AF. As the population ages, there is increased risk of developing AF. Future studies on the incidence of AF should include long-term cognitive assessment. Similarly studies undertaken to assess treatment of AF should include dementia as an outcome measure.

Smoking

Research in the 1990s suggested an inverse relationship between cigarette smoking and AD. These results are controversial and a subject of debate. A meta-analysis by Graves *et al.* showed a statistically significant inverse relationship between prevalence of smoking and number of pack-years to incidence of AD (125). Further data from the Rotterdam study showed evidence that the protection afforded by smoking cigarettes was only significant in ApoE ε4 carriers with a family history of dementia (126). This apparent protection could be due to regulation of nicotinic cholinergic receptors in the brain (127) or a nicotine-mediated reduction of amyloid formation (128). Strong arguments were made regarding the increased risk afforded by smoking as a vascular risk factor and its impact on stroke and VCI (129), even if it did supposedly protect against AD. It was also suggested that survival bias was responsible for the larger pool of cognitively impaired nonsmokers, and that this factor was not corrected for in the risk-benefit assessment of smoking (130).

There have since been various studies that have shown that smoking increases the risk of both AD and VCI (131–133). A recent meta-analysis showed that current smoking conferred a relative risk of 1·27 for any dementia and approximately 1·8 times the risk for both AD and VCI compared to nonsmokers (134). Rusanen *et al.* have recently demonstrated that heavy smoking (in excess of two packs per day) doubles the risk of dementia, AD, and VCI compared to those who have never smoked (135).

There are no long-term studies of cessation of smoking on cognitive outcome.

Elevated plasma homocysteine

There is evidence that elevated homocysteine is associated with an increased incidence of cardiac disease (136), carotid stenosis (137), and stroke (138,139). It has also been shown that homocysteine levels increase with age (140). Elevated plasma homocysteine may be due to deficiency of folate, vitamin B6, or vitamin B12. However, significant homocysteinaemia has been reported in cognitively impaired elderly who had normal folate and B12 levels (141). It is unclear how homocysteinaemia impacts upon the development of dementia, but it is likely that the effect is mediated through vascular risk and metabolic changes associated with aging (142,143).

Subsequently, an association was shown between elevated homocysteine and dementia. Seshadri *et al.* found that elevated levels of homocysteine were associated with an RR of 1·4 (95% CI (1·1–1·9)) for developing dementia and RR of 1·8 (95% CI (1·3–2·5)) for AD (144). Levels of homocysteine above 14 μmol/L were found to double the risk AD. Similarly Ravaglia *et al.* have shown that levels of homocysteine above 15 μmol/L were significantly and independently associated with a risk of developing dementia (HR = 2·08 (95% CI 1·31–3·30)) and AD (HR = 2·11 (95% CI 1·19–3·76)) (145).

There are negative studies showing no association between homocysteine and dementia. Initial data from The Rotterdam study showed no evidence of an association between increased homocysteine and dementia (146). However, the Rotterdam scan sub-study provides evidence that elevated homocysteine is associated with lower cognitive performance in elderly non-demented patients. There were no changes seen in the hippocampal region on MRI of the brain in these patients (147).

Studies evaluating correction of elevated homocysteine with vitamin supplementation have produced conflicting results. A Cochrane review of the effects of B6 supplementation showed no improvement in cognitive function (148). Another review assessed the effects of folate supplementation with and without B12, and found no consistent evidence of improved cognitive function. However, there was a positive response seen in AD patients who were on anticholinesterase medication (149).

ApoE

ApoE is a glycoprotein responsible for lipid transport in the brain and other organs. It exists in three isoforms (E2, E3, and E4) encoded by three alleles (ϵ2, ϵ3, ϵ4) on chromosome 19 (150). The single nucleotide polymorphism responsible for the allelic variant confers considerable difference in terms of function and associated risk of disease (151). The frequencies of these alleles in the general populations are 5–10% for ϵ2, 65–70% for ϵ3, and 15–20% for ϵ4 (152). Following the discovery of ApoE in amyloid plaque (153), the ϵ4 allele was found to be a significant genetic risk factor in the development of sporadic AD (154). Subsequently, it has been estimated that a single ϵ4 allele increases the risk of AD approximately three times, while two alleles confer up to 12 times the risk compared to noncarriers (155). The role of ApoE ϵ4 on AD risk appears to be related directly to Aβ metabolism. Recent reviews have explored possible mechanisms of ApoE ϵ4 on the increased production of Aβ, impaired clearance, and reduced transport axonally or across the blood brain barrier (152,156,157). In addition to an increased risk of AD, ApoE also increases the risk of vascular disease. As a result of impaired cholesterol transport and metabolism, both ApoEϵ2 and ApoEϵ4 accelerate atherogenesis and is known to increase risk or worsen outcome in a variety of conditions including head trauma, coronary surgery, stroke, and other neurodegenerative diseases (151).

Is there an additive risk due to the effect of ApoE ϵ4 on specific vascular risk factors? As mentioned earlier, the result from the HAAS suggests a significant increase in the risk of developing AD in diabetic patients who are ApoEϵ4 positive aside from showing a greater burden of AD-associated brain pathology (95). There is also evidence from the Kungsholmen Project that diabetes is a risk factor for developing AD only in the presence of ApoE ϵ4 (100). The relationship between ApoE4 and cholesterol appears complex. The effect of raised cholesterol as a risk factor for AD appears more pronounced in patients who were AopE ϵ4 negative (158).

Although ApoE ϵ4 increases the risk of developing AD significantly, there is as yet no definitive mechanism by which this is known to occur. It should also be noted that the presence of the ApoE ϵ4 genotype does not automatically mean that the carrier develops AD and neither is the presence of ApoE ϵ4 noted in all patients with AD.

Conclusion

In the coming decades, physicians will see a marked increase in the number of cognitively impaired stroke survivors. This will be especially true among the elderly. Ten per cent of patients who have suffered a single stroke and 30% of recurrent stroke survivors will develop cognitive impairment before the age of 85 years. Currently, AD and VCI are responsible for approximately 90% of dementia. It is likely that many stroke survivors will in fact suffer from an overlap of AD and VCI referred to as MD. MD is estimated to account for approximately 50% of current dementia cases. A more precise estimate of the proportion of patients with MD will only be possible if large-scale community-based studies of stroke and dementia incorporate histopathological evaluation. The current standard of diagnosis based on clinical and imaging criteria is not sufficiently sensitive to distinguish between the two conditions. Histopathological evaluation is therefore important given the synergistic relationship among NP, NFT, and vascular lesions. Although these conditions seem to be clinically (albeit marginally) and histopathologically distinct, the common ground of shared risk factors cannot be overlooked.

The role of vascular risk factors in the development of dementia appears to be independent of the risk associated with increased stroke. The established risk factors of hypertension, diabetes, raised lipids, AF, smoking, and, more recently, hyperhomocysteinaemia and ApoE have been shown to increase the risk of dementia independent of increased stroke risk There is evidence that the presence of more than one risk factor has an additive effect on this risk. This additive or perhaps synergistic effect would seem especially true of diabetes and ApoE. Vascular risk factors appear to exert their influence in midlife many years before dementia becomes apparent. This may explain why trials aimed at evaluating the effect of treatment of vascular risk factors on subsequent development of dementia have been mostly negative. Whether these negative results are a true reflection of a lack of response to treatment or whether the evaluation of treatment is assessed too late in the course of the disease is difficult to assess. The results of large, long-term epidemiological studies such as HAAS, Rotterdam, CAIDE, and the Kaiser Permanente study show that dementia risk can be lowered later in life if vascular risk factors are treated in midlife. The choice of therapeutic agent used in the treatment may also play a part in the response seen. This appears to have been true in trials assessing treatment of hypertension, diabetes, and hyperlipidaemia.

Current evidence is sufficient to support aggressive treatment of most vascular risk factors. However, studies evaluating the relative risk of these factors on developing dementia are still required. Further knowledge regarding these conditions may lead to new treatment targets and therapy guidelines. Further trials are also required to assess suspected vascular factors as they become apparent. Inclusion of imaging modalities in stroke and dementia should also be considered in future trials. The ability to image amyloid and

tau and assess functional brain activity using Single-photon emission computed tomography (SPECT) has provided further scope in dementia research. The use of both these imaging modalities has provided breakthroughs in our understanding of the pathogenesis of AD and FTD. It now remains to utilize these modalities to better our understanding of VCI. Cross-sectional and longitudinal studies of stroke patients using Pittsburgh Compound B (^{11}C-PiB) with comprehensive neuropsychological assessment will be a means of assessing VCI and the probable role of amyloid in its pathogenesis.

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